N-Terminal pro-B-type natriuretic peptide in the diagnosis of acute heart failure

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Background

The accurate and timely diagnosis of acute heart failure can be challenging, therefore national and international guidelines recommend natriuretic peptide testing to aid in the diagnosis. Despite these recommendations, NT-proBNP testing has not been universally implemented, in part, due to concerns about clinical utility in a real-world setting. Studies investigating the diagnostic performance of NT-proBNP have mainly been performed in relatively small, selected patient cohorts, limiting the generalizability of study findings across clinically important subgroups, such as older patients and those with renal disease or obesity; characteristics that are becoming increasingly prevalent in patients with heart failure.

Purpose

1. To evaluate the diagnostic performance of guideline-recommended NT-proBNP thresholds for acute heart failure across patient subgroups.
2. To develop and validate a decision-support tool that combines NT-proBNP concentrations with clinical characteristics

Methods

We performed a systematic review and requested individual patient-level data to evaluate the diagnostic performance of NT-proBNP thresholds in patients with suspected acute heart failure using random-effects meta-analysis.

Using this data, we developed and validated a decision-support tool (Collaboration for the Diagnosis and Evaluation of Heart Failure [CoDE-HF]) using a generalized linear mixed model (GLMM) to compute a value (0-100) that corresponds to an individual patient's probability of acute heart failure. We performed ten iterations of 10-fold cross-validation to generate the CoDE-HF score for each patient.

Results

Fourteen studies from 13 countries provided individual patient-level data in 10,365 patients in whom 43·9% (4,549/10,365) had an adjudicated diagnosis of acute heart failure. The negative predictive value of guideline-recommended rule-out threshold of 300 pg/mL was 94·6% (95% confidence interval 91·9%-96·4%), and the positive predictive values for age-specific rule-in thresholds (450, 900 and 1,800 pg/mL) were 61·0% (55·3%-66·4%), 73·5% (62·3%-82·3%) and 80·2% (70·9%-87·1%) respectively. Performance was lower in older or obese patients and those with prior heart failure *(Figure 1)*.

Our decision-support tool, CoDE-HF (**https://code-hf.shinyapps.io/code-hf/**) had good discrimination and calibration in patients with and without prior heart failure (area under the curve of 0·863 [0·848-0·878] and 0·931 [0·925-0·938], and Brier scores of 0·121 and 0·094 respectively). In 6,204 patients without prior heart failure, the decision-support tool identified 42·2% as low-probability (negative predictive value 98·5%, 97·6%-99·1%) and 30·5% as high-probability of acute heart failure (positive predictive value 75·0%, 67·6%-81·3%) *(Figure 2)* with consistent performance across subgroups.

Figure 1. Negative predictive value of the NT-proBNP threshold of 300 pg/mL across patient

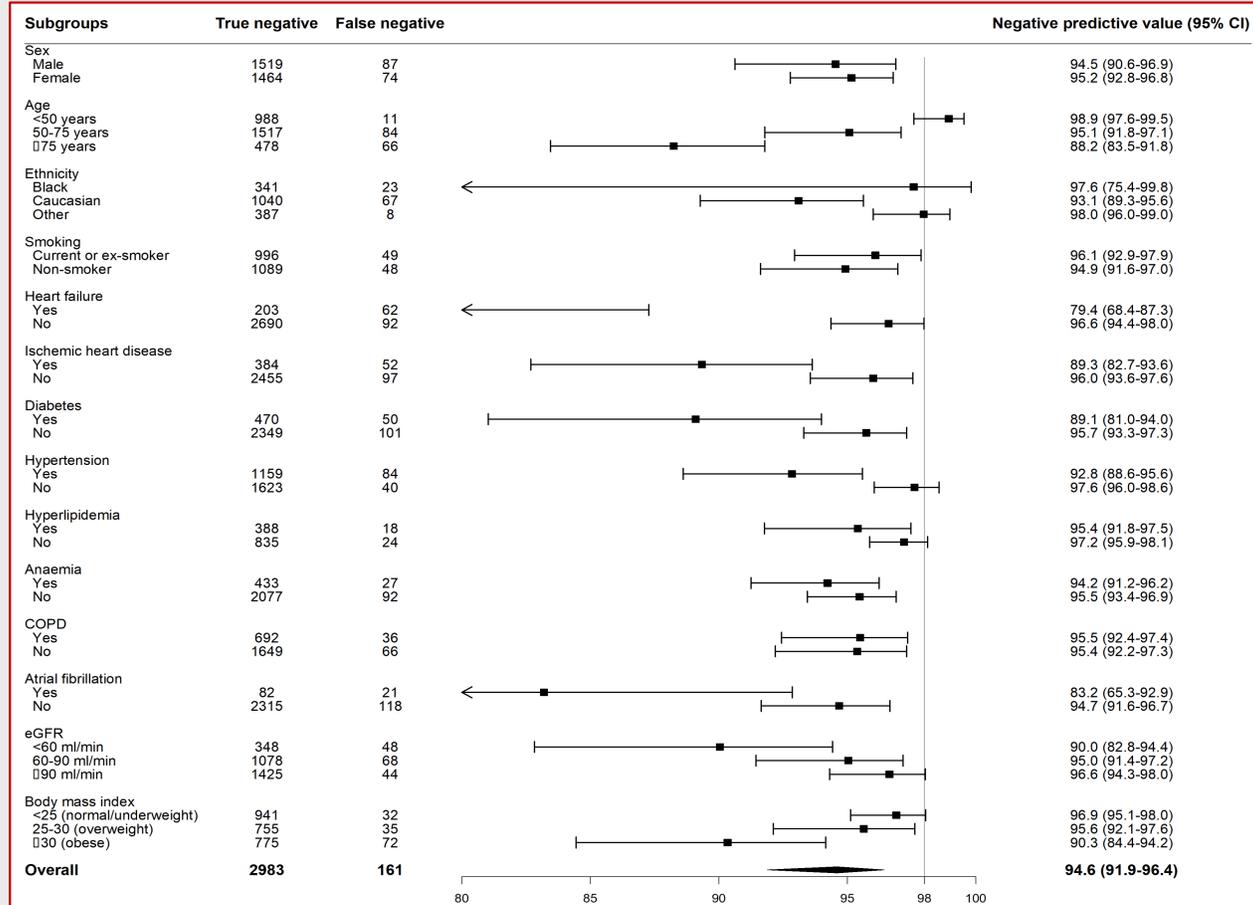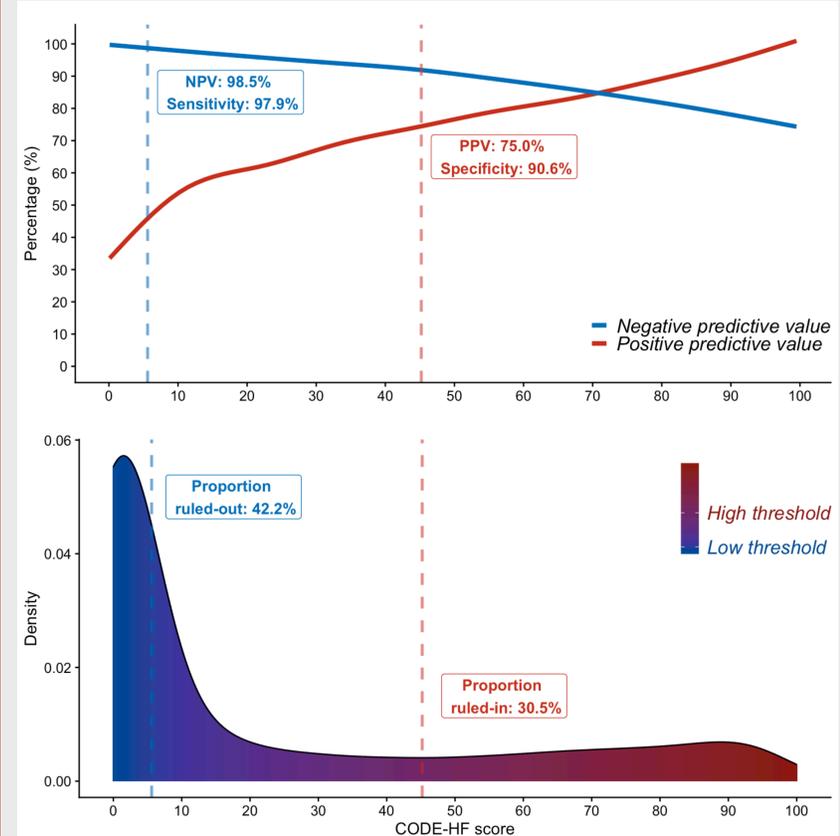| Subgroups	True negative	False negative		Negative predictive value (95% CI)
Sex				
Male	1519	87		94.5 (90.6-96.9)
Female	1464	74		95.2 (92.8-96.8)
Age				
<50 years	988	11		98.9 (97.6-99.5)
50-75 years	1517	84		95.1 (91.8-97.1)
≥75 years	478	66		88.2 (83.5-91.8)
Ethnicity				
Black	341	23		97.6 (75.4-99.8)
Caucasian	1040	67		93.1 (89.3-95.6)
Other	387	8		98.0 (96.0-99.0)
Smoking				
Current or ex-smoker	996	49		96.1 (92.9-97.9)
Non-smoker	1089	48		94.9 (91.6-97.0)
Heart failure				
Yes	203	62		79.4 (68.4-87.3)
No	2690	92		96.6 (94.4-98.0)
Ischemic heart disease				
Yes	384	52		89.3 (82.7-93.6)
No	2455	97		96.0 (93.6-97.6)
Diabetes				
Yes	470	50		89.1 (81.0-94.0)
No	2349	101		95.7 (93.3-97.3)
Hypertension				
Yes	1159	84		92.8 (88.6-95.6)
No	1623	40		97.6 (96.0-98.6)
Hyperlipidemia				
Yes	388	18		95.4 (91.8-97.5)
No	835	24		97.2 (95.9-98.1)
Anaemia				
Yes	433	27		94.2 (91.2-96.2)
No	2077	92		95.5 (93.4-96.9)
COPD				
Yes	692	36		95.5 (92.4-97.4)
No	1649	66		95.4 (92.2-97.3)
Atrial fibrillation				
Yes	82	21		83.2 (65.3-92.9)
No	2315	118		94.7 (91.6-96.7)
eGFR				
<60 ml/min	348	48		90.0 (82.8-94.4)
60-90 ml/min	1078	68		95.0 (91.4-97.2)
≥90 ml/min	1425	44		96.6 (94.3-98.0)
Body mass index				
<25 (normal/underweight)	941	32		96.9 (95.1-98.0)
25-30 (overweight)	755	35		95.6 (92.1-97.6)
≥30 (obese)	775	72		90.3 (84.4-94.2)
Overall	**2983**	**161**		**94.6 (91.9-96.4)**

Figure 2. Diagnostic performance of the CoDE-HF score in patients without prior heart failure

NPV: 98.5%
Sensitivity: 97.9%

PPV: 75.0%
Specificity: 90.6%

— Negative predictive value
— Positive predictive value

Proportion ruled-out: 42.2%

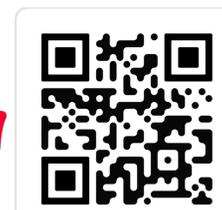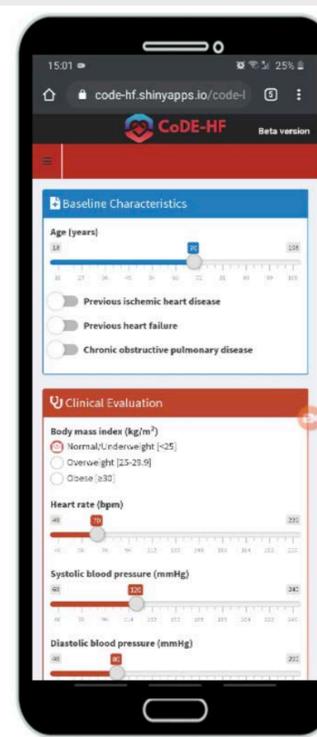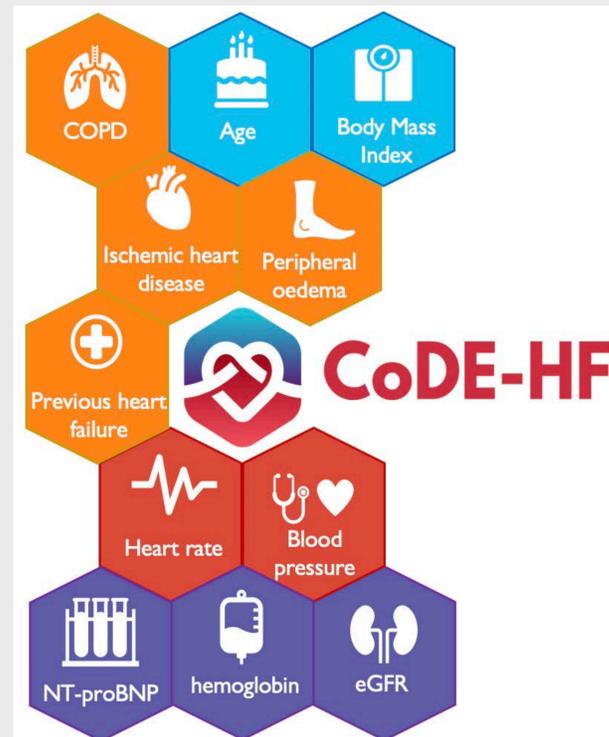Proportion ruled-in: 30.5%

High threshold
Low threshold

Conclusions

- To our knowledge, this is the largest study evaluating the diagnostic performance of NT-proBNP for acute heart failure to date.
- The diagnostic performance of NT-proBNP thresholds for acute heart failure varies across important patient subgroups.
- We developed and validated the CoDE-HF score, which combines NT-pro-BNP as a continuous measure with clinical variables to determine the probability of acute heart failure for individual patients. This decision-support tool accurately ruled-in and ruled-out acute heart failure and performed consistently across all subgroups.
- Prospective studies are now required to evaluate the impact of implementing this decision-support tool on healthcare resource utilization and patient outcomes.

Acknowledgements

COPD · Age · Body Mass Index · Ischemic heart disease · Peripheral oedema · Previous heart failure · Heart rate · Blood pressure · NT-proBNP · hemoglobin · eGFR

CoDE-HF

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